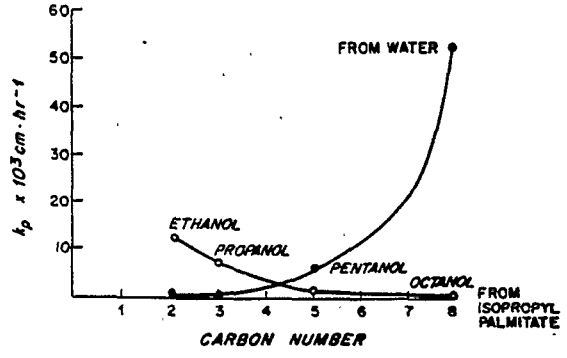

Fig. 58-9 Effect of vehicle on the permeability constant of the alcohols (From Scheuplein and Blank, 1971)

has an affinity for both water-soluble and lipid-soluble compounds. The bifunctional solubility of the tissue arises from its inherently mosaic, filament-matrix ultrastructure which allows aqueous and lipid regions to exist separately. This structure and its unique, encompassing solubility characteristics cannot adquately be duplicated over the full range of polarity by any single solvent. However, butanol and 50–50 mixtures of ethanol–water approximate the solvent character of the stratum corneum fairly well; and when lipophilic substances are applied from these vehicles, K_{MV} values are not too different from unity and preferential solubility effects are minimized. These principles are illustrated further by the data in Table 58-2 in which the permeability constants of the same molecules in different vehicles are compared. It is evident that the influence of vehicles can be enormous: *p*-ethylphenol, a very lipophilic substance penetrates 4000 times faster from water than from 95% ethanol; *N*-nitrosodiethanolamine, a water-soluble substance, penetrates 200 times faster from isopropyl myristate (olive oil) than from water.

It is evident from equation (13) or (15) that diffusional resistance of the stratum corneum (R_M) decreases as K_{MV} increases while the resistance of the stagnant, aqueous tissue layers R_T remains unchanged. If K_{MV} is increased by adding more methylene groups, eventually the diffusional resistance of the stratum corneum (R_M) will decrease to a point where R_T is comparable. At this point (approximately at C_{10} for the alcohols), the aqueous tissue layers become rate limiting and further increases in lipid character do not increase penetration (Yalkowsky & Flynn, 1973; Scheuplein, 1978).

ELECTROLYTES

Electrolytes applied from aqueous solution do not penetrate the skin readily. The ionization of a weak electrolyte has long been known to radically decrease its permeability; the much greater permeability of salicylic acid than sodium salicylate has often been discussed (Malkinson & Rothman, 1963). Quantitative data are scarce since very few ionic permeability constants have been successfully measured. Tregear (1966) lists only sodium, potassium, bromide (Wahlberg, 1965, 1968a, 1968b), and aluminum ions and all these permeability constants are approximately the same (i.e., $k_p \simeq 10^{-6}$ cm h^{-1}). The penetration rates of sodium and bromide ions through excised skin are not significantly different from their counterparts *in vivo*. Wahlberg has compared the relative penetration of ten ionic compounds through live guinea pig skin; he finds little or no differences in their relative permeabilities (Wahlberg, 1965, 1968a, 1968b). The permeability of chromium compounds through isolated epidermis was studied by Samitz et al. (1967), and surprisingly large fluxes and lag times of approximately 4 h were obtained.

These data are insufficient to provide a base for understanding ionic permeability through skin. Two obvious factors would tend to decrease ionic mobility within the tissue: (1) the stable hydration sphere around an ion that makes it virtually a polyhydroxylic ion and a much larger diffusing unit than a water molecule; and (2) the charge on the ion that is capable of interacting with coions, counterions, and fixed charges in the tissue. The first factor makes it likely that is the absence of a potential gradient, no ion will penetrate faster than water itself and very likely much slower. Much more work is needed in this area particularly on the effect of ion size, degree of hydration, charge, and potential difference on permeability before the physics of the diffusion process can be understood. Because the overall rate of ionic transport is low and seems to be nonselective, shunt diffusion through the appendages probably plays a very significant role. The relative rapid transport of histamine, charged dyes, and ferrous ion into skin by electrophoresis is almost certainly the result of permeation through the appendages (Abramson, 1940, and Gorin, 1940; Konecng, 1968).

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